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# **Regulatory Objectivity in Action: Mild Cognitive Impairment and the Collective Production of Uncertainty**

**Tiago Moreira, Carl May, and John Bond**

## **Abstract**

In this paper, we investigate recent changes in the definition and approach to Alzheimer's disease brought about by growing clinical, therapeutic and regulatory interest in the prodromal or preclinical aspects of this condition. We explore how clinical and research actors, in collaboration with regulatory institutions and pharmaceutical companies, come to frame these domains as uncertainties and how they re-deploy uncertainty in the 'collective production' of new diagnostic conventions and bioclinical standards. While drawing as a background on ethnographic, documentary and interview data, the paper proposes an in-depth, contextual analysis of the proceedings of an international meeting organised by the Peripheral and Central Nervous System Drug Advisory Committee of the US Food and Drug Administration to discuss whether or not a particular diagnostic convention - Mild Cognitive Impairment or MCI - exists and how best it ought to be studied. Based on this analysis we argue that the deployment of uncertainty is reflexively implicated in bioclinical collectives' search for rules and conventions, and furthermore that the collective production of uncertainty is central to the 'knowledge machinery' of regulatory objectivity.

**Keywords: Alzheimer's Disease; biomedicine; diagnostic convention; mild cognitive impairment; uncertainty.**

In the last decade, there has been increased interest in the biomolecular and epidemiological characterization of pre-clinical dementia. It is argued that early diagnosis of dementia and particularly of Alzheimer's Disease (AD) will facilitate the prevention of dementing processes and lower the prevalence of the condition in the

general population. The search for a diagnostic category or biomarker that would serve this purpose is an ongoing endeavour for research and clinical communities. This research, however, has been problematic, leading some commentators to argue that the categories and standards that support the work of clinicians and researchers ‘reveal increasing ambiguity rather than clarity’ (Gaines & Whitehouse, 2006: 62), in that boundaries are becoming less certain than before between normal aging and dementia, on the one hand, and different types of dementia -- Vascular dementia, Lewy-Body dementia or Fronto-temporal dementia-- on the other.

In this paper, we investigate how clinicians and researchers, in collaboration with regulatory institutions and pharmaceutical companies, come to frame these uncertainties and re-deploy them in the ‘collective production’ of new diagnostic conventions and bioclinical standards. Our point of departure is that such practices are concerned with a distinctive type of objectivity, regulatory objectivity, that focuses on the establishment of conventions through collectively concerted programs of action (Cambrosio et al. 2006). This form of objectivity is particularly suited to the complex, non-linear relationships established between laboratory biology and the clinic in contemporary medicine, in which hybrid *bio-clinical* entities are set up to mediate the relationship between those settings (Keating & Cambrosio, 2003). In this context, the establishment of conventional standard and systems of regulation are viewed as endogenous requirements for ongoing knowledge production, innovation and clinical work rather than forms of external control. Here, we offer a detailed view of the collective, reflexive work that is entailed in making such conventions.

The paper focuses on one such conventional standard: Mild Cognitive Impairment (MCI). MCI is a concept originally coined by the American neurologist Ronald Petersen to describe a transitional stage between normal cognitive aging and dementia (Petersen et al. 1999; Petersen, 2003). Our interest in it is that it was also explicitly devised as an attempt to *bridge* emerging biomolecular models of Alzheimer’s disease progression with secondary prevention therapies being devised in laboratories at the turn of the 21<sup>st</sup> century and the perceived increase in the presentation of ‘mild memory problems’ in the clinic around the same period (Petersen et al, 2001). According to this view, MCI was to bring together the laboratory and the clinic into one common ground of understanding Alzheimer’s disease. That this view was not generally and immediately accepted in the field of dementia research, practice and policy provide us with the opportunity to analyse an

aspect of regulatory objectivity that has remained hitherto unexplored: how are conventional standards put together. In the paper, we explore the processes through which conventional standards are proposed, criticised, evaluated and re-configured to serve the purpose of a diverse and changing configurations of actors and settings. While drawing on ethnographic, documentary and interview data documenting the scientific, clinical and political controversy around MCI,<sup>i</sup> the paper analyses one single turning point in this process: the proceedings of an international meeting about MCI organised by the Peripheral and Central Nervous System Drug Advisory Committee of the US Food and Drug Administration (FDA) in 2001 (Food and Drug Administration, 2001). The policies and agenda laid at this meeting came to shape most of the subsequent basic, clinical and therapeutic research in this area as well as the clinical guidelines and consensus groups held on MCI to this day (Petersen et al. 2001; Winblad et al. 2004; Gauthier et al. 2006). Furthermore, in this meeting, for the first time in its history, the FDA asked one of its committees ‘to address some fundamental aspects of a particular diagnosis ..., and decide if it exists and how best it ought to be studied’ (Food and Drug Administration 2001), rather than considering a licensing application for a specific drug. As such, this meeting constitutes an important resource not only to understand the history of MCI as a conventional bioclinical entity, but more importantly to examine regulatory objectivity *in action*.

The main finding of this analysis is that actors’ assessments of ‘evidence’ and reflexive engagement with conventional aspects of their practice, which Cambrosio and colleagues consider central to regulatory objectivity, are both embedded in an ongoing ‘collective production of uncertainty’. We argue that uncertainty should be understood not merely as the ‘context of’ bioclinical collectives’ search for rules and conventions but also as an achievement endogenous to -- and essential for -- the dynamics of those collectives (Bourret & Rabearisoa, 2008).<sup>ii</sup> From this perspective, uncertainty is not a socio-cognitive ambivalence experienced by individuals in complex decision-making situations (Fox, 1959; Fox, 2000). Our empirical focus is on the practical accomplishment of uncertainty, on two levels. First, we are interested in uncertainty as a way of framing the organisation of knowledge production, technological development and policy formulation in domains characterised by controversy and indeterminacy (Callon, 1998). In the first section of this paper, we describe how epistemic, technological and political changes in the field of AD worked together to unsettle the relations between laboratories, clinics, and regulatory and

policy institutions established at the end of the 1970's. We will then suggest that the emergence of prodromal dementia categories, such as MCI, can be seen as attempts to wane the proliferation of uncertainties in this domain<sup>iii</sup>, and that, in this respect, the FDA 2001 MCI meeting represents a key collective effort to frame this process. This last point relates to our second understanding of uncertainty as a discursive, interactive accomplishment. Here, we draw from Lynch's (1998) homology between the lines of interrogation of evidence deployed by lawyers in the OJ Simpson 1994-95 trial and the modes of enquiry employed by academic STS. His analysis of lawyers' 'deconstructive' investigations of forensic DNA profiling as a sociology of knowledge machine provides an insight into the power of settings such as courts in transforming and unsettling stable socio-technical arrangements. But while Lynch's investigation was anchored on STS' conceptual opposition between stability and uncertainty, our focus was on how participants in the FDA meeting collaboratively exposed the uncertainties and the *historical contingencies* of the conventions that support their activities at one particular time *in order to* construct another explicitly contingent category. In the main section of the paper, we examine how this was achieved by a) predicating the exploration of uncertainties about MCI upon the definition of the political boundaries for the collective, b) redistributing uncertainty to adjacent domains, and c) drawing from this extended uncertainty to formulate a policy of articulation between research and clinical practice based on the transience of MCI as a category. Through these procedures, actors invested an uncertain and transient conventional category with the power to mediate and organise the exploration of indeterminacies and ambiguities about dementia and its treatment. We suggest that the collective production of uncertainty should be seen not as the reverse but as constituent to the temporary stabilisation of biomedicine's knowledge and entities in the clinic, laboratory and regulatory fora. In these types of setting, STS' lines of enquiry might be more useful than they have been in the courts (Lynch and Cole, 2005)

### **Bioclinical Uncertainty in Alzheimer's Disease and Related Dementias**

In the historiography of Alzheimer's disease (Ballenger, 2006), it is generally accepted that the re-awakening of interest in senile dementia in the 1960's was sparked by the publication of studies led by Martin Roth and colleagues at Newcastle

(UK), which correlated the number of neuritic plaques in patients' brains with the scores obtained by those patients in cognitive tests (Roth et al. 1966). Developments in electron microscopy in the early 1960's had fostered a re-description of the neuropathological features of dementia at the ultra-structural level (Kidd, 1963; Terry, 1963) and this created interest in neurobiology among neuropathologists. This interest reshaped Alzheimer's disease during the 1970's, and was the basis for a number of etiological theories that were proposed in that decade, the most important of which addressed the possibility of a scrapie-like virus, toxic effects of aluminium in the brain and a deficit of the neurotransmitter acetylcholine. This last hypothesis, supported by neurochemistry studies that linked the cholinergic system in the brain and the cognitive deficits observed in patients suspected to have Alzheimer's disease, became the focus of a considerable proportion of the Alzheimer's disease research in the late 1970's and early 1980's (Davies & Maloney, 1976; Perry et al. 1977; Whitehouse et al. 1982).

These advances in the understanding of the biology of the disease were accompanied by an intensive process of characterization of the disease processes from a clinical/behavioural perspective. Already in synchrony with the Newcastle correlation studies, Blessed, Tomlinson and Roth had developed an informant-based instrument to assess memory, concentration and orientation (Ballenger, 2006). This was followed by a series of tools aiming to measure mental status, such as the Mini Mental Status Exam (Folstein et al. 1975), tests concerned with 'clinically observable deterioration' such as Global Deterioration Scale (GDS) (Flicker et al., 1991), and others aimed at assessing behavioural changes, or cognitive performance. The multiplication of instruments, the establishment of the Alzheimer's Disease Research Centres in the US and, in part energized by these new centres, the perceived increase in demand for dementia care, created the context for a consensus conference that set criteria for the clinical diagnosis of AD (McKhann et al. 1984). The establishment of this 'conventional standard' supported clinical diagnoses of AD, which themselves embodied a vision of the integration between research, therapeutic experimentation and clinical practice (Moreira, in press).

This envisioned coherence was, however, not solely the product of a spontaneous self-organising process between research and clinical constituencies. In a crucial way, this coherence had been framed and shaped by the efforts of the National Institute of Aging (NIA), particularly after the nomination of Zaven Khachaturian as

Director of the Neuroscience and Neuropsychology of Aging Program in 1977, which enveloped these constituencies, political actors and the ‘American public’ within what Robert Butler, the founding director of the NIA, called the ‘health politics of anguish’ (Fox 1989). The ‘politics of anguish’ and the activities of the Alzheimer’s Association were key in the NIA’s efforts to obtain budget increases from the US Congress, as well as its efforts to crystallize a new political understanding of old age and its changing dynamics (Holstein, 2000). In this context, it was possible for this bioclinical collective to establish itself in the public arena, with further the assistance of expert calculations of the dimension of the ‘problem of dementia’ in the US (Katzman, 1976).

The alignment between the worlds of research, clinical practice, politics and patient advocacy that underpinned the emergence of the bioclinical collective for AD was, however, built upon shifting foundations. The same molecular techniques that had first energised AD research in the 1970’s were already, during the 1980’s, suggesting possible alternatives to the ‘cholinergic hypothesis’; alternatives that were linked to the therapeutic implications of the solubility of amyloid in the neuritic plaques found in brains of patient with Alzheimer’s disease (Glenner & Wong, 1984). Also it was becoming clear that expectations, fostered during 1970s and 80s, for a ‘rational’, unproblematic translation of the cholinergic hypothesis into safe pharmacology were unrealistic. When results of clinical trials of cholinesterase inhibitors (ChEIs) started surfacing in the 1990s, the expectations in the clinical research community had been already significantly lowered (Moreira, in Press). Drawing on a genetic model of the pathogenesis of early-onset AD, the bioclinical collective of AD appeared, during the 1990s, to focus its attention and therapeutic hopes on what became known as the ‘amyloid cascade hypothesis’ (Hardy and Higgins, 1992). Despite its success, controversy about the validity of the theory increased over the years, as competing theories were proposed that emphasized the role of the tau protein in the formation of axonal ‘tangles’ (Lovestone & Reynolds, 1997), upstream oxidative stress (Nunomura et al. 2006), or the dynamics of protein folding.

This multiplication of hypotheses was further compounded by the evolving relationship between different types of dementia. While the definition of AD proposed the during the 1970s relied on its differentiation from the vascular models of dementia that had been popular before (Ballenger, 2006), during the 1990’s new work

demonstrated that vascular pathologies, notably atherosclerosis, white matter lesions, and mid-life arterial hypertension, were associated with AD and could enhance cognitive loss (Humpel & Marksteiner, 2005). Furthermore, research on the biology of dementia with Lewy bodies, Parkinson disease dementia, and fronto-temporal dementia led to a redefinition of the classification of the dementias. In this classification, AD shared characteristics with both amyloidopathies, such as Familial Amyloid Polineuropathy (Corino de Andrade's Disease), and taupathies, such as fronto-temporal dementia, or progressive supranuclear palsy. These trends, it was increasingly realised, could potentially lead to the disaggregation of the 'identity' of the AD and its bioclinical collective.

Those concerned with the clinical diagnosis and management of AD had to deal with different problems. While the establishment of the 'conventional standard' for the diagnosis of AD (McKhann et al., 1984) and the arrival of ChEIs helped to consolidate and stabilize the category of AD itself, the striving towards reliability and consistency across AD clinics may have produced a paradoxical effect. From the beginning, clinical assessment tools such as the GDS had included milder-than-dementia levels of cognitive impairment and seemed to suggest a continuous path in this condition. In fact, a debate about whether AD is qualitatively different from normal aging or quantitatively different along a cognitive continuum had been alive since the 1980's (Brayne & Calloway, 1988; Anonymous, 1989). The introduction of standardized criteria for the diagnosis of AD in 1984, however, excluded persons presenting with 'mild memory problems'. Thus, in the next ten years there was a multiplication of terms to categorise the 'forgetfulness' experienced by a growing number of patients perhaps affected by increased public awareness of the cognitive symptoms of AD: Age Associated Memory Impairment (Crook & Larrabee, 1988); Mild Cognitive Impairment (Flicker et al. 1991), Age Related Cognitive Decline; Age Associated Cognitive Decline and Cognitive Impairment, No Dementia.

Another consequence of the establishment of standardised diagnostic criteria for AD was the emergence of fractures within the space of representation for dementia. As a variety of professions became involved in the care of AD patients, different accounts of the reality of AD and the needs of patients started surfacing. One of most significant of these fractures resulted in the emergence of a coherent psychosocial model of dementia in the late 1980's developed by Tom Kitwood and others (Kitwood 1993). This psychosocial model criticized the biomedical model of



dementia (Bond, 1992), and generated a concern for patients as a 'persons'. It changed the focus of research and drew attention to patients' personal needs, and has underpinned much of the criticism about the imbalance of attention and investment between the two main axes of the dementia health policy: the 'search for a cure' and the organisation of 'care'.

### **Mild Cognitive Impairment and 'the FDA Meeting'**

In the past decade or so, the AD bioclinical collective appears to have experienced fundamental uncertainty at all levels, from the understanding of the basic pathogenesis of the condition, to clinical practice and health policy. These uncertainties cannot be understood in absolute terms, but only in relation to the coordination achieved in the field during the 1980's, on the one hand, and the emergent agreement within the collective that only preventative strategies could tackle the progression and lower the prevalence of AD, on the other. Despite their multiplicity, most of the hypotheses circulated in the field have attempted to identify the 'first event' in the pathological process leading to clinical dementia, and have suggested therapeutic approaches to halt the progression. This perspective encouraged increased interest in identifying pre-clinical stages of dementia (Lock, 2006). In this process, prodromal dementia categories were positioned as possible re-articulations between different types of laboratories – molecular biology, neuropathology, neuropsychology, neuroimaging, etc. -- and the clinic, in an attempt to 'cool down' or stabilise some of the uncertainties discussed in the last section.

One of the most successful re-articulations was the concept of Mild Cognitive Impairment. Originally conceived as a specific stage on the GDS scale (Flicker, Ferris et al. 1991), it was only in the end of the 1990's that, by the hand of Ronald Petersen and colleagues at the Mayo Clinic, Rochester, it came to be embody such potential for intermediation between the laboratory and the clinic (Petersen, Smith et al. 1999).

This is well exemplified in the justification given for the concept of MCI in an important review of the concept

Basic research, such as the identification of secretase inhibitors and the development of an immunization model for the prevention of amyloid deposition, underscores the importance of developing techniques for early

detection (of AD). Parallel with these endeavours, clinical research aimed at identifying the earliest signs of cognitive impairment has progressed. ...

Mild cognitive impairment deserves recognition and further study because, as preventive treatments for AD become available, it will become incumbent on clinicians to identify persons at risk of AD and those with the earliest signs of clinical impairment. (Petersen et al. 2001)

In its original formulation, MCI defined a transitional stage between normal cognitive aging and dementia. As a syndrome it consists of the clinical presentation of a memory complaint, accompanied by an objective memory impairment (assessed by clinical interviews, psychological and brain imaging tests), but absence of any other cognitive impairment, and essentially preserved activities of daily living. MCI also excludes the diagnosis of dementia (Petersen et al. 1999). Based on longitudinal controlled studies of clinical populations, MCI identifies individuals 'at risk of dementia'. The aim of MCI, at this point in time, was mainly to identify a population for research on the bioclinical antecedents of dementia and, as the quote suggests, to test the effectiveness of preventative therapies for AD.

This definition had considerable success in attracting the interest of the AD research community (see Figure 1): from 1999 to 2004 the number of publications on MCI increased six fold, in fields ranging from clinical genetics, to epidemiology, neuropsychology, and neuroimaging. Pharmaceutical companies, many of which funded a significant proportion of the research on MCI, were interested in the possibility that the new category would enable researchers to target a population suitable for a new generation of drugs.

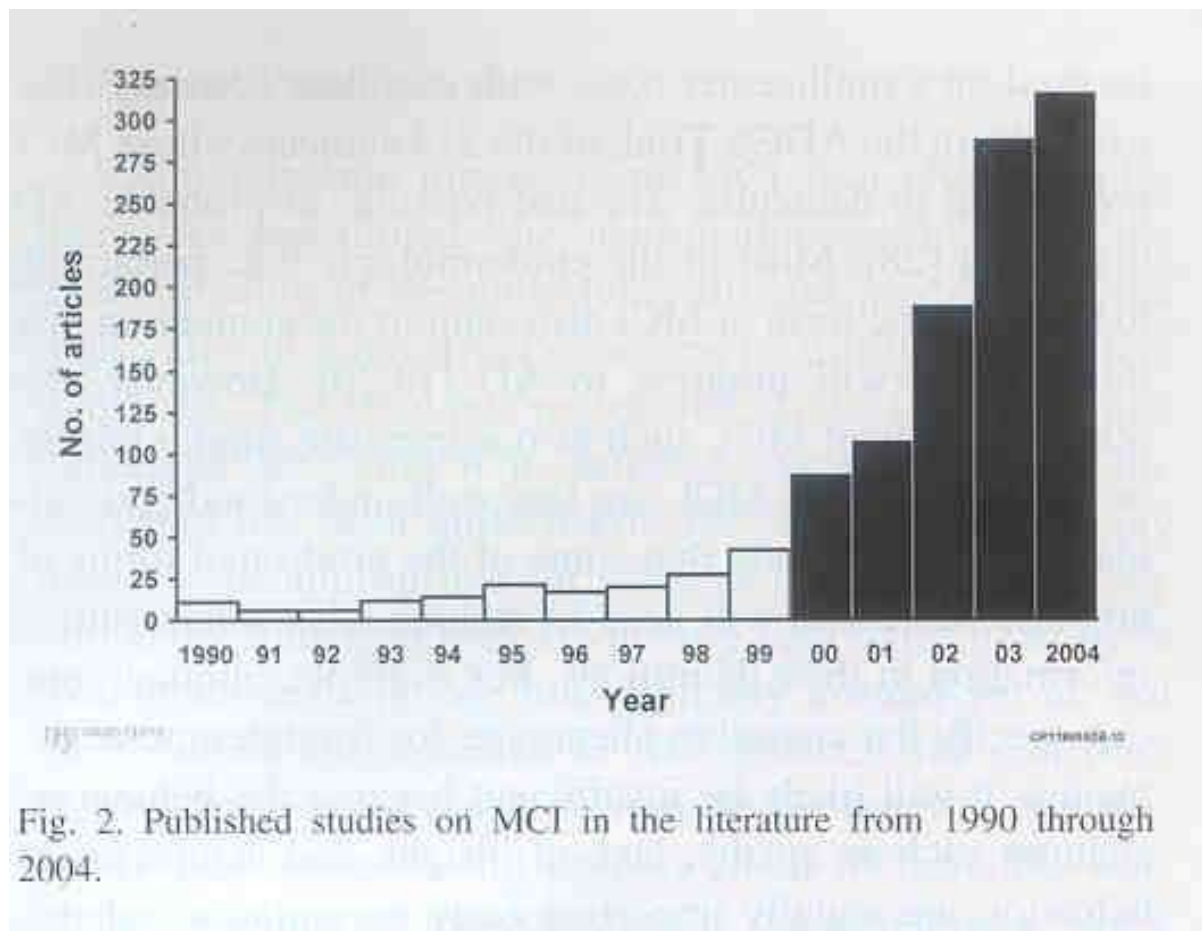


Fig 1: Source (Petersen 2005) Reproduced by kind permission of the author.

As was suggested in the last section, the shifting understanding of the pathogenesis of AD, combined with the ‘modest’ clinical effects of ChEIs, led to a re-orientation of basic and therapeutic research. It was thus possible to observe that, during the 1990’s this bioclinical collective moved towards a new therapeutic vocabulary that emphasized the ability for molecular compounds to be ‘disease modifying’ (Moreira, in Press). Research groups became increasingly interested in finding pharmacological agents that would target the molecular mechanisms that precede neuronal death (amyloid aggregation, etc). This trend also encapsulated the idea that these agents would only be effective when used before such pathological molecular processes manifested themselves clinically. It is widely recognised that it is very difficult to evaluate such therapies, both because they are more likely to off-set the risk-benefit ratio acceptable for non-symptomatic individuals involved in clinical trials, and because they require larger, longer and more expensive types of trial design (see, for example, Citron, 2004).

From this perspective, MCI presented itself as a possible ‘bridge’ between previous designs used in this field and new trial designs. If it would be possible to find, through this transitory design, whether a drug could be meaningfully evaluated, the next steps towards funding longer, larger trials could then be taken. If this scenario seemed probable, and even desirable for pharmaceutical companies, their researchers and their academic collaborators, they had only one problem. MCI was not at that time (circa 2000) recognised as a clinical entity by any of the international or professional disease classifying institutions.<sup>iv</sup> There was thus uncertainty about whether the results of ongoing trials would have any meaning for drug approval institutions such as the FDA.

MCI also presented new opportunities for ChEIs marketing licence holders. Because there was an accepted view that ChEIs had moderate effects on cognitive abilities and clinical symptoms of dementia, it was possible to argue that such effects would be more significant in milder stages of the disease. This obviously would also represent an extension of the market for ChEIs. In addition, in previous years there had been controversy about whether the outcomes chosen by the FDA to evaluate anti-dementia drugs – change in cognitive scores plus one global measure of functioning (Leber, 1990) – were the most appropriate given that, as one coalition of researchers put it, ‘[t]he maintenance of baseline levels in ... Alzheimer’s disease may be a more relevant goal to ... individual patients than transient cognitive improvement’ (Winblad et al. 2001: 656). From this perspective, MCI could become an important tool to trace the evolution of these baseline scores in a population at ‘risk’. The recognition of MCI patients as a ‘target population’ by the FDA, in fact, would be an important step in changing the evaluation framework that was (and still is) seen to constrain the evaluative performance of ChEIs.

MCI brought together the interests of a multiple array of actors and constituencies who identified the FDA as a crucial mediator in this process. This was materialised in a number of requests to the FDA by companies asking to develop treatments for MCI (Food and Drug Administration, 2001: 10). This created a particular problem for the FDA because its approval of any specific product is linked, through the Federal Food, Drug and Cosmetic Act, to how the product is presented in its ‘product label’ and, as Dr. Katz, representing the FDA, said in his opening address to the meeting, to ‘whether or not the population for whom the drug is intended can be unambiguously described’ (Food and Drug Administration, 2001: 11). The FDA thus

had to take the unusual step of assessing the validity, reliability and sensitivity of a bioclinical construct, and of evaluating whether the existing ambiguities of the concept were likely to disappear or increase.

In order to take that step, the FDA's Peripheral and Central Nervous System Drugs Advisory Committee organised a meeting to which it invited a panel of FDA experts, public speakers and an audience. 'The FDA meeting', as it subsequently came to be known by researchers and practitioners in the field, was held on 13<sup>th</sup> of March 2001, and included presentations by eight experts, who were selected by the FDA on the basis of contributions to research on MCI. They were: Dr. Petersen, the neurologist who proposed the term in its current use; Dr. Dekoski, neurologist and advocate of the clinical application of a PET scan approach to dementia biomarking (Lopresti et al. 2005); Dr. Duara, a neurologist known for his view that MCI is a general syndrome associated with various pathologies (Loewenstein et al. 2006); Dr. Reisberg, a geriatric psychiatrist particularly concerned with the clinical significance of subjective memory impairment (Flicker et al. 1991); Dr. Ganguli, general psychiatrist and epidemiologist of dementia, a 'friendly sceptic' towards the concept (Ganguli et al. 2004); Dr. Ferris, a psychologist, collaborator of Dr. Reisberg; Dr. Shah, psychologist and proponent of the cognitive testing approach to dementia screening; and one representative of an European drug development team, Dr. Waegemans. In addition, various (mainly expert) participants in the audience were allowed to ask questions to the panel.

The panel and speakers were asked to answer and discuss the following questions: a) Can MCI be clearly defined in a clinical setting? b) Are there valid criteria for the diagnosis of MCI? c) Can MCI be distinguished from Alzheimer's Disease and other causes of dementia? d) What outcome measures are appropriate to use in clinical drug trails conducted in MCI? and e) Should clinical drug trials in MCI incorporate any special features in their design? Although biomolecular and other basic researchers were not present at the meeting, the discussions were framed by the need to articulate new biomolecular models of AD with clinical practice, including the possibility of using biological 'surrogate markers' such as brain imaging or CSF analysis as measures in clinical trials.

## **The Collective Production of Uncertainty**

The FDA meeting's agenda was aligned with the emerging epistemic and biomedical expectations of the collective that were referred to in the beginning of the last section. In setting the meeting, its organisers were required to 'translate' these expectations and processes into a confined space (Callon, 1986). This transposition entailed the coordination of persons, spaces and materials that together could 'make present' the complex interrelations of a bioclinical collective. In this 'the FDA meeting' shared a number of characteristics with clinical practice guideline development meetings, in particular the focus on the interaction between the discussion within the meeting and the 'outside world', both as *context of production* of the issues discussed in the meeting, and as *context of reception* of the documents and policies assembled at the meeting (Moreira, 2005). It thus became acutely important to establish temporal and symbolic linkages between those contexts. Analysis of the transcript of the FDA meeting suggests that this was achieved in three steps, albeit not sequentially. The boundary between the context of the meeting and the meeting itself was built through the (mainly discursive) enactment of a link between the uncertainties surrounding the category of MCI and the group of experts assembled at the meeting. How the participants maintained this link throughout the meeting is the focus of the first subsection below. If the participants had not attempted to extend uncertainty to other, hitherto unopened black boxes, this might have threatened the correlated solidarity of the confined collective assembled at the meeting. This redistribution of uncertainty is the focus of the second subsection. The third subsection explores how participants drew from this extended uncertainty to articulate a policy to link research and clinical practice, based on the transience of MCI as a category. This policy could be the reason why the FDA meeting became a turning point in the history of MCI and the AD bioclinical collective.

### *Putting a Fence Around a Mystery*

The main challenge the FDA faced in preparing this meeting was to balance the representation of the various perspectives about MCI proposed in the field with the need to achieve an accountable outcome within the given time constraints. The choice of speakers thus followed a policy that Dr. Katz summarised in his opening remarks to the meeting,

MCI, as you know has been characterised variously in the literature but, *in general, it is a condition* that is described as occurring in elderly patients who predominantly have a memory impairment ... and patients are considered neither to be normal nor to have dementia but their cognitive status falls somewhere in between. (Food and Drug Administration, 2001: 10, our emphasis)

Dr. Katz reduces the range in perspectives on MCI, including those that questioned the utility of trying to describe it in the first place, by accepting that '*in general, it is a condition*'. This re-description of the epistemic status of MCI in 'the literature' allows him to bring together the participants in the meeting because it makes visible the difference between 'out there' and 'in here' by confining the level of uncertainty that the meeting will take into account. The micropolitical significance of this policy is important to note: it enables the collective exploration of the uncertainty and controversy about MCI at the meeting to be guarded against outright challenge or deconstruction. Having established this, Dr. Katz then goes on to say that,

In the case of MCI there is not unanimity in the literature about the diagnostic criteria that can reliably identify patients who are alleged to have the condition. So, as I say, one of the critical questions we would like you to address is whether or not you believe that there does exist a set of criteria that can be readily applied by practitioners and that can reproducibly and reliably identify patients presumed to have MCI. (p. 11)

The shift in the epistemic status of MCI from 'a condition' to an 'alleged' reality or 'presumed' diagnosis is striking. But Dr. Katz does more than just deepen the doubt that he and the FDA are prepared to cast upon MCI, he also sets up the basic rules of the 'sociology of knowledge machine' of the meeting (Lynch, 1998). The selected presenters are asked to give their views of whether or not they 'believe that there does exist a set of criteria' to identify MCI against a sceptical panel. This format is familiar to the FDA members, who apply it to assess and *deconstruct* claims made by pharmaceutical companies about drugs. In the context of this 'unusual' meeting, however, the questioning could not be solely focused on the strength of the claims presented to the Committee, as the links that support the reliability of MCI were in question from the very beginning. In effect, it appears that the FDA's usual machinery

was put in the service of exploring the possible and expected articulations between research and practice that different versions of MCI might offer. This is observable, for example, in the Q&A that followed Dr. Petersen's presentation.

DR. KAWAS: Actually, I would like to ask a question of Dr. Petersen, and it has to do primarily with the issue of defining this entity out in the clinical setting. ... [I]n the clinical setting what instruments would you recommend that the clinician be using to identify these individuals? Would it be the four that you showed us and the ones that we use in the research environment, or what are your thoughts on that?

DR. PETERSEN: That actually is a very important issue and a difficult one because while I think it is a readily identifiable condition, that is, there are a fair number of people who fall into this, I am not necessarily convinced that it can be identified in a quick and dirty fashion. [In a clinical trial] we are using the Mini-Mental State performance above 24. ... Then, we are using a memory tool, paragraph recall .... Again, that is not the end-all, be-all but I think it takes something like that. I don't think it can be done quickly in the office setting. (p. 46)

Dr. Kawas' question deals with the possibility of extending the detection of MCI in contexts other than the research settings where it was originally formulated. As Dr. Petersen's reply makes clear, Dr. Kawas is interested in knowing what forms of work support this diagnostic convention. In Dr. Petersen's opinion, the diagnostic work that produces MCI cannot be easily extended to 'the office setting' in primary or non-specialist care. This might explain the difference between what he estimates to be the 'number of people who fall into this' category and those who were actually identified at the time of the meeting. By suggesting that MCI requires a specialist setting to be identified, Dr. Petersen is also advocating a way to address the uncertainty that had lingered and still lingers over MCI: managing and perhaps reducing this uncertainty in the 'expert' setting of AD centres.

The transportability of MCI thus became one of the central points of debate within the meeting, not only because it focuses on the uncertainty about whether or not MCI 'really exists', but also because it offers different answers to the questions posed by the FDA about clinical trial design. This link was explicitly made in a question to Dr. Ferris by Dr. Wolinski, one the member of the FDA committee:



DR. WOLINSKY: I guess one of the things that I am struggling with is ... if you could actually construct a trial and were lucky enough to have a pharmacologic agent, carried out in careful clinical settings, that actually delayed the progression from phase I to phase II, or whatever we call this, and the person on the street can only diagnose phase II and we don't know whether starting the drug at phase II will prevent progression to phase III, what do we then do when we have a drug for which no one can make a diagnosis except in very rigorous, well-defined confines? (p. 98)

A similar point is addressed by Dr. Ganguli later in her response to a question posed by Dr. Duara:

DR. GANGULI: Well, I share your view about the [existence of a cognitive] continuum, and my understanding of why we are discussing this conversion is only to try and find out an appropriate endpoint for an MCI trial. My view as a clinician is that I can already treat somebody off-label if I think that he has incipient AD. I don't really need to have the FDA or DS to say that MCI is a non-indication. So, if the question is how do we better define this condition for its own sake so we understand the pathology, that is one thing. If you are saying how do we define it as an indication for drugs, that is a question I am not qualified to answer. (p. 131)

In Dr. Ganguli's view of the link between these two issues is evidently problematic: by putting the two together, the FDA and, for that matter, the rest of the presenters, were defining MCI as a suitable stage to test and probably use new, preventative therapies for AD. For her, the question of whether or not MCI is an entity 'out in the trenches' precedes the formulation of a therapeutic or public health strategy. Following this exchange, various participants suggest possible estimations of prevalence of MCI in the general population, none of them actually supported by data, which leads Dr. Kawas to the conclusion that 'what we need to do to find the estimate that people are looking for is to go back to the trenches' (p. 138).

The FDA's 'sociology of knowledge machine' appears to have worked here to reduce the conflict between the two versions of how to define the uncertainty of MCI. Furthermore, the co-existence and proposed synchronicity of a programme of

epidemiological research with a programme of therapeutic research also represents a different approach to the management of uncertainty proposed by Dr. Ganguli. While hers is a staged approach where the contours of the problem have to be defined before thinking how to tackle it, the FDA's proposal was one of maximising possible uncertainties. Importantly, the FDA proposal also opened up the possibility of a future alignment between the epidemiology of MCI, its extended clinical use as diagnostic category, and the implementation of therapeutic strategies. One important aspect of this policy of opening a future where differences might coordinate is that it relied on cautious surveillance over the black boxing processes during the meeting. Near the end of the meeting, Dr Van Belle, a member of the committee, alludes to such black boxing with a reference to putting 'a fence around the mystery':

DR. VAN BELLE: I think we have defined a mystery. We have sort of put a fence around the mystery but we have really heard many ways of defining MCI today and I am not sure that there is a consistent operational entity that we can deal with at a relatively simple level. ... I am not sure that it is very useful from a clinical point of view to try to do something like this at a national level. From a research level, an institution or a group could come to some agreement as to how they are going to define operationally such an entity and then do some research on that. But in terms of really having a clinical entity, I just haven't seen the evidence yet. (p. 205)

Dr. Katz's view was not much different:

At least by some definition as I understand the Petersen criteria, there really is no functional impairment. Other people have different definitions of MCI that do include functional impairment. So, you know, we are sort of back to 'do we all know what we are talking about when we say MCI?'. (p. 258)

The significance of these interventions has to do with the interaction between what Dr. Belle called the 'fence' and the 'mystery'. The discursive production of the mystery within the meeting was deployed through an exploration of the uncertainties surrounding MCI – whether it is one thing or a complex syndrome with

heterogeneous symptoms, whether it is early AD or an entity in itself, etc. The committee's dissatisfaction with the answers provided by the speakers enabled the participants to widen the collective that was concerned with this 'entity's' probable existence: whereas at the beginning of the meeting, MCI was located within a few research clinics, the exploration of uncertainties in the relation between these sites and the 'real world' (of everyday clinical practice) or epidemiological and biomolecular research provided a new, extended set of possible relations for MCI.

The successful management of this collective exploration of uncertainty depends upon the construction of boundaries for the collective. As Michel Callon and Vololona Rabearisoa (1998) have argued, this task is intrinsically political, as it relates to the ability to stabilise a 'forum' of debate and, through its procedures of debate, to determine the collective's extension and composition in a form of dynamic containment. The composition of the 'fence' that Dr. Belle was referring to is thus intimately associated with his suggestion that 'an institution or group should come to some agreement'. Similar suggestions were reiterated throughout the meeting. Together, they lead us to the view that the FDA committee was attempting to establish a continuity between this meeting and future meetings as a basis for the extended collective they had just reshaped. This was achieved through a careful articulation between different types of uncertainty.

### *Redistributing Uncertainty*

The collective production of uncertainty about MCI at the FDA meeting and the correlated establishment of procedures and actors to manage it was itself a risky strategy. Why would the FDA and the collective they supported be invested in a 'mystery'? How could this collective know that the mystery would become less mysterious through this strategy? In order to address this practical problem, participants in the meeting collectively reflected about key established conventions in this field, and in particular the criteria for diagnosis of AD. This entailed looking into the 'black box' of the very definition of AD: the association of clinical diagnosis of dementia with the neuropathological diagnosis post mortem confirming the presence of neuritic plaques and neurofibrillary tangles.

Dr. Kekoski's presentation highlighted this issue as follows:

In [a neuropathological correlation study], [Dr. Davis] looked at his cases that had the postmortem CDR of 0.5 -- now we are moving to the

... transition stage that [Dr. Petersen] discussed .... In this particular case, when Davis looked at his postmortem CDRs, about 60 percent of these cases would have met criteria for Alzheimer's disease at autopsy. In our study of the cases, again about 60 percent of these cases also had evidence of AD. There is a bit of a paradox here. All of our [MCI] cases would get a diagnosis of possible AD under CERAD [neuropath] criteria. Again, *we are a victim of our definitions*. To have a CERAD definition of definite AD by autopsy you must have evidence of dementia in life. So, we have a logical contradiction here. We cannot say these patients had dementia in life; they are the MCI cases. So, if they had enough plaques to make a diagnosis by CERAD criteria of dementia the highest they can get is a possible AD diagnosis. They would have to have had evidence of dementia in life and those path changes to get definite AD. (pp. 55-56, our emphasis)

The consortium to establish a registry for Alzheimer's disease (CERAD) had proposed standard neuropathological criteria for the postmortem diagnosis of AD (Mirra et al. 1991), which by 2001 was generally accepted and used, particularly in the US. However, as Dr. DeKosky makes clear, the neuropathological diagnosis of AD depends upon a prior clinical diagnosis of dementia. The clinical diagnosis of MCI, or of an equivalent 'transitional stage', introduces a degree of uncertainty to this process, in that it is possible for non-demented patients to meet the CERAD neuropath criteria for AD. This contradiction makes visible the conventionality of the clinical standard for AD diagnosis. In Dr. DeKosky's view, the constraining powers of the category become more significant than what they facilitate, thus making researchers and clinicians 'victims' of their own definitions.

Questioning the adequacy of the clinical standard for AD diagnosis became a recurrent strategy in the participants' discussion. Later, in the open discussion section of the meeting, Dr. Chui, of the University of Southern California, summarised the issue:

Dr. CHUI: ... I think that because MCI is the frontier now we might be assuming that the diagnosis of Alzheimer's disease is firm. We have dropped the terminology probable Alzheimer's disease, possible Alzheimer's disease, and here we are just using Alzheimer's disease.

Some of us have acknowledged that we are saying clinical diagnosis of Alzheimer's disease. The Alzheimer's disease centers have shown that when you look at pathology as the gold standard the clinical diagnosis of Alzheimer's disease is fairly sensitive in research settings but it is not specific. The sensitivity among 28 centers, collectively contributing over 2000 cases of dementia, was about 93 percent sensitive but only 55 percent specific. So, the accuracy was about 85 percent. If you use that in evidence-based dementia terms, the likelihood ratio is about 4, which isn't considered a very good diagnostic test. (pp. 223-24)

One particularly interesting aspect of this strategy is how the 'firmness' of the clinical standard for the diagnosis of AD is undone by referring to other standards -- the CERAD criteria or, in Dr. Chui's case, evidence-based medicine criteria for grading diagnostic procedures (Sackett et al. 2000). The problematic nature of the AD diagnostic standard could then be compared with the problems the FDA committee was exploring in relation to MCI diagnostic criteria. This suggested that accepting the uncertainties of MCI would require acknowledging the quasi arbitrariness of AD (Whitehouse, 2001). That the focus of this comparison was the clinical setting should not be surprising because it is in such settings -- the Alzheimer's centres -- that the participants had invested hope in finding consistency and validity for MCI. Furthermore, this amounted to a challenge to the FDA's approved labelling of dementia drugs based on clinical trials of patients diagnosed with AD through those criteria. Some of the participants in the FDA meeting seemed to be suggesting that if the ambiguity of MCI was reason for the FDA to be cautious about extending labelling of existing drugs, so should the ambiguity of AD have been a barrier to their approval in the first place.

The solution to this challenge led participants to explore the historicity of their conventions. Interestingly, it was left to the representative from the 'real world', Dr. Ganguli, to identify the problem:

[We] are all quite familiar with [the criteria for MCI by now] but ... I would like to focus your attention on number five for the moment, which is what do we mean by not demented? We are, as [Dr. DeKoski] said, victims of our own criteria. We are victims of these dementia criteria. The NINCDS criteria were published in 1984. They say that

you cannot have onset of AD after age 90. Well, this is 2001 and I have patients who were perfectly fine until the age of 92. What am I supposed to call them? Are we going to *be locked in forever into these criteria* that were written, you know, in good faith 20 years ago? We have learned a lot since then. Are we allowed to move the criteria along because it is not just where does normal aging cross over into MCI; it is also when do we say that they are now demented? (p. 121, our emphasis)

Dr. Ganguli suggested that she was facing a new clinical reality, perhaps underpinned by changes in the incidence of cognitive aging in the population between 1984 and 2001. Moreover, there had been a change in the knowledge base about the rates of cognitive aging expected at particular ages. Whereas in 1984, it seemed inadequate to categorise an individual as demented if s/he was over 90 years of age, because most were likely to have symptoms of dementia, in 2001, there was a clear distinction between individuals of that age group who became demented and those who did not. She thus offered a new interpretation for why the constraining aspects of the conventional standards used in AD appeared to be strengthening: the inadequacies of the NINDS criteria (McKhann et al. 1984) were the result of the historical changes in the 'object' and the knowledge about AD. It was not a case of a fundamental flaw with the criteria: times had changed and so should conventions.

Recognising the historicity of conventions came to have crucial importance for developing the discussion. It brought into focus the temporal aspects of processes of adoption of conventions in research and clinical communities. Documenting the history of the uptake of AD diagnosis criteria allowed participants to, once more, draw equivalences between AD and MCI. The possibility of conducting clinical trials on MCI or using MCI in the clinic was a matter of time:

DR. KAWAS: And, if drugs were to be used for [MIC], how would you imagine training the clinicians to do the same thing?

DR. WAEGEMAN: That is always the difference between the ideal situation of a clinical trial and real life, but I think it was already mentioned today that ten years ago, twenty years ago there was a difficult problem in diagnosing dementia. We think that we have now

solved this problem. Maybe in five years time we will be a lot further in teaching how to diagnose MCI. (p. 188)

Dr. Kawas' interest in the possibility of MCI being used in the clinic is couched in the idea that not only does MCI take work to be made visible but also it takes work to shape this form of diagnostic criteria. This is also contained in Dr Waegemans' reply, which emphasised the time lag that takes to make conventions usable in the clinic. Such an understanding of AD diagnosis was unproblematic for most of the participants, who had experienced the process of implementing the NINCDS criteria during their professional training or practice. From their perspectives, the adoption process was independent from the problems of diagnostic accuracy for AD. It was as if participants were suggesting that it was possible to implement consistent diagnostic conventions regardless of their accuracy.

By highlighting the historical character of diagnostic criteria for AD, participants at the FDA meeting shifted the burden of responsibility on MCI proponents. It was then possible to ask, as did Dr. Duara 'are we applying an unreasonable standard ... to MCI when we are [asking] do we have well defined standards?' (p. 278). One important consequence of this change, in light of what was argued in the last section, was that the uncertainty of AD diagnostic criteria became part of the wider problem for the collective in which MCI was the key mediating entity. Embracing AD diagnosis in the MCI strategy of uncertainty management meant also that this collective was not only concerned with differences on a synchronous level, but also was committed to re-writing the history of AD. As one of us has argued elsewhere, drawing on the case of neurosurgery, the production of dis/continuities in the history of collectives is essential for the practical achievement of 'innovation' (Moreira, 2000). Similarly, to make MCI possible, AD had to become close to being a contingent outcome of history.

### *The Strength of Transient Entities*

There were however consequences from investing in this strategy of extended uncertainty for MCI itself. If AD diagnostic criteria were a product of the past, who could say that the same would not happen to MCI in a few years time? Why would clinicians need to question something that, despite its inaccuracies, still 'did its job', and why shouldn't they trust MCI as a category if there was no certainty about its

foundations? The remarkable solution that participants devised for this problem demonstrates how conventions are integral for action and for generating knowledge within bioclinical collectives (Cambrosio et al. 2006). Answering one of the FDA panelist's question in his presentation, Dr. Ferris argued that,

MCI broadly speaking is a heterogeneous syndrome. However, homogeneous groups representing prodromal AD or other subtypes can, I think, reliably be identified. MCI trials can examine disease progression or at least clinical progression and provide a bridge in drug development between symptomatic trials and the ultimate goal of disease prevention trials. (p. 94)

While, as we know, the FDA committee was not prepared to agree with Dr. Ferris' version of the diagnostic reliability of MCI criteria, his proposal that MCI trials become a 'bridge between symptomatic trials and the ultimate goal of disease prevention trials' seemed acceptable. Of course, by accepting this proposal, the FDA committee also would be agreeing that MCI is an indication for the drugs tested in those trials. This might have been construed as a direct challenge to Dr. Katz's contention, discussed earlier, that the FDA must adhere to the Federal Food, Drug and Cosmetic Act, except for the fact that the committee had first-hand knowledge of the convoluted relations between nosological knowledge and therapeutic evaluation. Dr. Temple of the FDA used the example of cardiovascular drugs to describe these relations:

I think the history of these kinds of difficulties is that you do the best you can, and that sometimes things happen to enable you to distinguish things that you formerly felt were the same better than you could before. Sorry to use another cardiovascular example, but we now know that heart failure comes in two flavours and that the treatments are widely different depending on whether your problem is the ventricular beat systolic function or filling, diastolic function. And, the drugs that work in one don't necessarily work in the other and might even be adverse. But for decades people didn't realize this and all of the above got included in clinical trials. That probably decreased the effectiveness of certain treatments but since we didn't know any better and the net effect was beneficial the drugs were approved for undifferentiated heart



failure. Now that we are smarter we won't do that anymore. So, the situation conceivably, I guess, could be the same here .... It wouldn't be the first time, and I am sure some of the people in later Alzheimer's disease trials really had something other than Alzheimer's disease. I mean, it is hard to imagine that diagnostic accuracy was a hundred percent. (pp. 234-35)

The interaction between knowledge of diseases and therapeutic research is such that clinical trials can only be described as (to paraphrase Dr. Temple) historical events. In the contingent situation surrounding the trial 'you do the best you can' in the knowledge that the concepts and data supporting the results may be incomplete or wrong. Thus, it is necessary to de-emphasise the need for an absolute fit between disease and drug, even when drugs are approved. What might seem like a sensible policy from the FDA's point of view, represents for the proponents of MCI an opportunity to employ the category as an entry point into clinical trials. It is significant, furthermore, that Dr. Temple, when drawing on the extended uncertainty discussed in the last subsection, accepts the precedent that in the AD field trials might have been conducted with patients who did not have that disorder. And the situation 'could be the same here' with MCI.

In order to understand why the FDA would be willing to support clinical trials in an ambiguous situation, such as with MCI, it is necessary to remind ourselves that the FDA committee had already established that the question of knowing what MCI was, was really a question of defining it as an indication for drugs. In Dr. Temple's intervention, the clinical trial figures both as a technique to test the effectiveness of drugs and as an heuristic tool to explore disease mechanisms. This concurs with Dr. Ferris proposition that MCI trials are a bridge between therapeutic 'paradigms'. If it was possible to conduct an MCI trial, one would be testing not only the drugs in question but also the design of the trial, and consequently the adequacy of MCI as an entry point, an indication for drugs and as diagnostic entity (Vos, 1991). The circularity of the process was predicated upon the ability to transfer the collective from one MCI 'paradigm' to another. If MCI were here to stay, it would lose its heuristic role..

It is important to stress that by accepting the heuristic, bridging role of MCI, the FDA meeting does more than legitimise an idea that was already in circulation in

the field for a few years. By transposing this proposal to the confined collective of ‘the FDA meeting’, participants linked this idea to a wider set of policies and programmes of action. Endorsing MCI as a ‘means of transportation’ for the AD bioclinical collective was closely aligned with the policies of articulation and extension of uncertainty discussed earlier. In effect, it could be argued that in ‘the FDA meeting’, what may have earlier been seen as three different aspects of MCI – its epistemic uncertainty, its relation to AD, and its status in trials of old and new treatments for dementia – had now become intertwined. The policies that came out of ‘the FDA meeting’ summoned basic, clinical and epidemiological researchers, drug developers, clinicians, patient associations and regulatory institutions to use MCI as a temporary *scaffolding device* that would align their different purposes and interests. As a temporary mediator, MCI would allow them to explore the uncertainties that concerned this collective.

The collective production of uncertainty is embedded in actors’ reflexive work on the historicity of conventional standards. This suggests that participants in ‘the FDA meeting’ were acting as ‘practical historians’ (Garfinkel in Lynch and Bogen 1996: 62) and that the collective production of evidence required actors to engage with the organisational and political work that assembled documented past and present conventions. Unearthing the contingent relations and processes that sustained the emergence of past conventions did not, however, lead participants to seek a more permanent foundation for the conventions they were creating. The transience of those conventions was in fact their main attraction, in that they were built to effect a transition between one stage and another, between one set of relations and another.

The influence of the policies endorsed in ‘the FDA meeting’ -- that MCI could be ‘tested’ in clinical trials -- would only become apparent in later years as research results surfaced, clinical trials were finished, and the research and clinical communities came to re-assess the epistemic value of MCI. However, what was to come was predicted in an interview for *Fortune* magazine by Harry Tracy, of the consultancy company Neuroinvestment, in his assessment that the FDA’s endorsement of MCI opened a ‘totally new landscape for developing memory drugs’ (Stipp, 2001). A measure of the accuracy of this prediction is the growth in the number of trials on MCI registered in the FDA sponsored on-line database (<http://clinicaltrials.gov/>): a 13 fold increase from 5 in 2000 to 46 on-going and

completed trials in 2007. These include trials of therapies previously licensed for AD, as well as new pharmacological compounds, and lifestyle and behavioural interventions. This can also be seen from the 76% increase in the number of publications on MCI between 2001 and 2002 (see Figure 1). But the most significant effect of this meeting was in how it set methodological standards for therapeutic evaluations of drugs for treating MCI (Jelic et al. 2006), which implemented the policies set at the meeting for exploring uncertainty.

A good illustration of this point concerns the announcement of the results of one of the first clinical trials using MCI as baseline diagnostic – a trial of Vitamin E and a cholinesterase inhibitor (Donepezil) led by Dr. Petersen and sponsored by the National Institute of Aging and Pfizer/Esai (Petersen et al, 2005)– which was discussed sceptically by expert audiences at international conferences between 2004 and 2006 (see endnote 1). While there was agreement that the trial had demonstrated negative results for primary end points – conversion from MCI to AD – most commentators have emphasised its success in designing and conducting a valid MCI trial. In an Editorial in the *New England Journal of Medicine*, where the trial was eventually published, for example, Deborah Blacker suggested that:

[r]ather than wait for new agents, Petersen et al. carefully evaluated the ability of two standard treatments for established Alzheimer's disease to slow the progression from mild cognitive impairment to frank Alzheimer's disease. ... The present trial represents a major step forward in the literature on trials of treatment for mild cognitive impairment. ... What lessons does the study by Petersen et al. offer clinicians and their patients with mild cognitive symptoms? First, symptoms of memory loss in older persons should be taken seriously, since they may represent the beginning of Alzheimer's disease, and — once more effective early interventions are available — it will be critical to ask patients about these symptoms and learn to recognize them as early as possible. (Blacker, 2005)

The clinical significance of MCI derived from its ability to produce measurable effects in a clinical trial. In this it might have helped that results were clearly – significantly -- negative for Vitamin E and – not so significantly – for Donepezil on the conversion of MCI to AD. Nevertheless, the circularity between

conventional standards, therapy and therapeutic evaluation (Vos, 1991; Lakoff, 2005: 173-74), which had been set up in the FDA meeting, resurfaced in a clear message by a leading medical journal endorsing the use of MCI in the clinic.

In addition, only by reference to ‘the FDA meeting’ is it possible to understand that, while or even before such general endorsement took place, the main proponent of MCI, Dr. Petersen, could write these words in the leading monograph on the topic:

Ultimately, MCI is likely to be a heuristic concept. It has generated and will continue to spawn research on aging and early cognitive impairment. At some point the term will be discarded and another will take its place. Hopefully, the concept will have contributed to an understanding of the spectrum of cognition from normal aging to AD (Petersen, 2003: 12)

Accepting the transience of MCI may have been the price its proponents had to pay for bringing it into the ‘real world’.

## **Conclusion**

Social science research on regulatory practices in medicine has examined changes in the social organisation of medical work, new forms of medical innovation, evidence-based medicine, shifts in professional autonomy, and the positioning of users. Analytical emphases tend to fall either on exogenous or endogenous drivers of regulation. The consolidation of biomedicine in recent decades has put the boundaries of medicine in question (Gaudilliere, 2002; Clarke et al. 2003; Keating & Cambrosio, 2003), and it is argued that regulatory bodies such as the FDA are integral to the dynamics of biomedicine (Cambrosio et al. 2006). This paper focused on how regulatory bodies fulfil such role by exploring how their ‘knowledge machinery’ frames the collective production of new diagnostic conventions and standards.

Our close analysis of the FDA meeting on MCI suggests that the deployment of uncertainty is reflexively implicated in bioclinical collectives’ search for rules and conventions, and that the collective production of uncertainty is in fact central to the ‘knowledge machinery’ of regulatory objectivity. We have shown that a) the reflexive achievement of uncertainty is predicated upon collectives’ (re)building of socio-technical boundaries, b) that these boundaries facilitate the re-opening of surrounding

epistemic, technical and social black boxes, and c) that it is possible for some collectives to reflexively agree on the temporary, historical nature of their foundations. We suggest further that the process we have described constitutes a general feature of biomedicine's epistemic and technological dynamics, in that the production and temporary stabilisation of biomedicine's knowledge and entities requires continuous 'uncertainty work' in the clinic, laboratory and regulatory forum.

This conclusion is relevant for understanding current changes in research, clinical management, and policy on dementia. As we have shown, in the aftermath of the FDA meeting, MCI came to embody the promise of new therapeutic developments and diagnostic practices for Alzheimer's disease. However, it could only do so by re-articulating the definition of AD. Some commentators even suggested that it has brought about the 'end' of AD (Whitehouse, 2001). There are benefits and drawbacks to such re-articulation. On the one hand, MCI contributed to an increased recognition of the uncertainty around the causes of AD and fostered research within a multifactorial framework in which specific and non-specific compounds – for example, statins (Panza et al. 2006) -- co-exist with lifestyle interventions for preventing (or delaying) dementia. On the other hand, the research and policy focus on MCI and upstream, precursor biomolecular events in the natural history of the disease has meant that downstream processes and symptoms are receiving less attention (and resources). This has resulted in a growing imbalance between the interests and needs of people who already have dementia or are close to developing it and those who will possibly benefit from preventative strategies in the future as a result of the changes in the field of dementia research.

Finally, the paper leads to the suggestion that in the exploration of uncertainties around and underpinning bioclinical conventions, actors and institutions could do worse than seek the assistance and collaboration of STS academics. Our attention to uncertainty, contingency and multiplicity could, in this particular setting, help not only in unearthing the links that tie present conventions together but also in building new, required supports for knowledge making and clinical work. This however might prove more challenging than the examination Cole endured in his admissibility hearing (Lynch and Cole, 2008) in that instead of positionings along dichotomies of belief and credibility, institutions might require 'proof' of enduring political commitment to the collective (see 'Putting a fence around a

mystery'). Accepting the stability of our alliances may be the price we have to pay for being able to explore the uncertainties of biomedicine from within.

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## Notes

<sup>i</sup> The study was undertaken between 2004 and 2006. Data were collected through: a) historical literature review on MCI and cognate concepts; b) participant observation of scientific conferences in the dementia field, c) semi-structured interviews with experts in dementia research, care and policy; d) observation of fieldwork in a dementia clinic and in neuropathology laboratory; e) symposia and research-user workshops. A systematic search strategy was used to identify relevant literature through MedLine (1350 refs). Conventional methods of historical research were used to identify key research papers. We developed ethnographic fieldwork at seven international biomedical conferences, which entailed qualitative, participant observation of communication in the relevant fields. We also conducted 37 interviews with international experts in dementia research, care and policy. These were qualitative semi-structured interviews on the scientific, clinical and societal meanings of MCI and/or early diagnosis and prevention of dementia. We used a stratified purposive sampling strategy, according to field of expertise, country and gender, having as main selection criteria the publication of relevant scientific, clinical or policy research on MCI identified through the literature review. In symposia and a research user workshop, potential users of the results of the project -- researchers, clinicians, carers and patients -- were invited to discuss the outcomes of the project and to consider how this research might move forward to influence and benefit older people with memory problems. See Moreira & Bond (2008), and Moreira, et al. (2008).

<sup>ii</sup> The concept of 'bioclinical collective' aims to capture the extended, heterogeneous, distributed character of the production of evidence that is required by the contemporary intersections between laboratory and the clinic. As the name suggests, such collectives are characterised by a concern around an hybrid entity or category that is neither wholly derived from clinical observation nor from laboratory experimentation (Keating and Cambrosio, 2003). The conceptual genealogy of the concept can be traced back to Callon and Law's (1995) notion of hybrid collective as an alternative to social network or 'society' because as Latour concisely explains, 'Unlike society, which is an artefact imposed by the modernist settlement, this term refers to the association of humans and non-humans. While the division between nature and society renders invisible the political process by which the cosmos is collected in one livable whole, the word collective makes this process central. Its slogan could be 'no reality without representation'' (Latour, 1999: 304). This concept was further developed by Callon and Rabeharisoa (1998) in their notion of the patient collective as an unfolding compositions of bodies, competences, representations artefacts, procedures and emotions gathered together by particular activities around a particular condition/illness. As with these concepts, the notion of bioclinical collective aims to emphasise the way in which links between heterogeneous entities are deployed in the representation --the convention in this case- that bring them into being. For this reason, who and what belongs to a particular collective and in what capacity is mostly an empirical that is related to the activity at hand.

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<sup>iii</sup> We thank Andrew Webster for having suggested this analytical proposition.

<sup>iv</sup> Although not explicitly, our analysis of the emergence of MCI draws as background previous work on the dynamics of classificatory systems and diagnostic categories. Of particular significance is Bowker and Star's (1999) work on how categories, when left alone, become embedded in practice, invisible as organising, political devices for those who use them. As Bowker and Star remark most professionals recognise the constructed, conventional nature of the categories and classificatory systems they use although these issue tend not to be explored collectively (Bowker and Star, 1999: 320). Our study exactly focuses on situations where it is necessary to conduct such exploration.

DRAFT: DO NOT QUOTE WITHOUT PERMISSION

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